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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/762,568	KATSUMANTA ET AL.
	Examin r	Art Unit
	Daniel M Sullivan	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *9-14 and 16-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 March 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 30 July 2001 as the U.S. national stage of international application PCT/JP00/02785 filed 27 April 2000, which claims benefit of Japanese patent application 11158351 filed 4 June 1999. The preliminary amendments filed 6 February 2001, 2 July 2002 and 14 August 2003 have been entered. Claims 1-18 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-8 and 15) in the Paper filed 14 August 2003 is acknowledged.

Claims 9-14 and 16-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Priority

Receipt is acknowledged of papers filed under 35 U.S.C. 119 (a)-(d) based on an application filed in Japan on 27 April 2000. Applicant has not complied with the requirements of 37 CFR 1.63(c), since the oath, declaration or application data sheet does not acknowledge the filing of any foreign application. A new oath, declaration or application data sheet is required in the body of which the present application should be identified by application number and filing date.

Drawings

The drawings are objected to for the reasons indicated on the attached PTO-948. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

Specification

The disclosure is objected to because of the following informalities:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. In particular, the word "Novel" is redundant in the context of an issued patent and should be removed from the title. The remaining title, "plasmid vector", is does not adequately describe the claimed invention.

Appropriate correction is required.

Claim Objections

Claim 8 is objected to because of the following informalities: The claim encompasses non-elected subject matter (i.e., a transgenic animal). The claim should be amended such that it is directed to the elected "cell having the plasmid" (see the Office Action mailed 16 July 2003, page 2). Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 8 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is directed to a transformant transformed using a plasmid vector. According to the discussion in the paragraph bridging pages 44-45, the transformant of the claims encompasses any somatic chimera or transgenic animal including humans. Thus, to the extent that it encompasses a genetically modified human, the claim is directed to nonstatutory subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transformant transformed with the plasmid according to claim 2, wherein said transformant is an isolated host cell or a transgenic chicken expressing a GFP transgene, and a method of producing a useful substance in a host cell *in vitro* or producing GFP in a transgenic chicken, does not reasonably provide enablement for transgenic animals, or methods of using transgenic animals, other than a transgenic chicken expressing a GFP. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: Claim 8 is directed to a transformant transformed using the plasmid vector of the invention. In the paragraph bridging pages 44-45, the specification states, "host cells into which the vectors of the present invention can be introduced...include cells in living plants and animals. When somatic cells of living animals are used as the host cells, somatic chimeras or [transgenic] animals can be produced and used to produce useful substances." Thus, the transformant of the claims encompasses somatic chimeras and transgenic plants and animals transformed to express any useful substance. As transformation of a host cell with the disclosed vector does not inherently produce a transformant having a definite phenotype, the transformant of claim 8 encompasses transgenic organisms having widely divergent phenotypes.

The method of claim 15 is directed to a method of producing a useful substance comprising introducing the plasmid vector of the invention into a host cell, allowing said vector to integrate into the genome of the host cell and expressing a protein encoded by the vector. In the paragraph bridging pages 45-46, the specification further indicates that useful substances includes any protein for which a DNA can be obtained, or any substances for which DNA can be obtained that encodes for an enzyme enabling the production of the substance. Thus, the claimed method is directed to a method of producing any protein or any substance that can be produced using an enzyme that is encoded by a DNA. With regard to production of useful substances *in vivo*, the specification provides non-limiting examples such as production of useful substances in the milk of mammals or in the eggs of birds (paragraph bridging pages 44-45). Thus, the claimed method is generic to a method of expressing any useful substance in mammals.

The specification also teaches that techniques for integration of a foreign gene into the genome of a host cell can be used in gene therapy to treat incurable diseases such as genetic diseases (see especially the paragraph bridging pages 8-9), cancer (see especially the first full paragraph on page 9), infectious diseases (see especially the paragraph bridging pages 9-10). Thus, the specification contemplates that the claimed method of integration of a foreign gene into the genome of a host cell *in vivo* can be used as gene therapy.

As the claimed method is not limited to expression of any particular useful substance and does not set forth method steps that direct the method to any particular purpose (i.e., the method steps are generic to any method comprising inserting a plasmid DNA into the genome of a host cell) the claim broadly encompasses production of any useful substance in a host cell or transgenic animal, or a method of treating any disease using gene therapy.

Amount of direction provided by the inventor and existence of working examples: The instant disclosure describes a plasmid vector comprising both an integrase gene operably linked to a promoter and an integrase recognition region, which facilitates integration of the plasmid vector into the genome of a host cell (see throughout). In the examples, Applicant demonstrates: a method of integrating a vector into the genome of a cell line transfected with the vector (Example 2); a method of integrating a vector into the genome of somatic and germline cells of chickens by injecting the vector into embryos (Example 3), and germline transmission of the vector (Example 6); a method of expressing a feline G-CSF protein in a cultured cell line by the method of introducing a vector comprising a nucleic acid encoding G-CSF (Example 4); and a method of expressing a marker gene (i.e., GFP) in transgenic chickens comprising injecting a vector comprising GFP into embryos.

With regard to using the broad scope of the transformant of claim 8, as it encompasses any transgenic animal transformed with the disclosed vector, the specification teaches only that the transformants can be used for production of useful substances. The specification then provides a discussion directed to heterologous expression of proteins in the eggs of transgenic chickens (see especially the discussion beginning on page 45 and continued through page 49). However, as the only limitation on the transformant is that it comprises the vector, using the full scope of the claimed transformants requires that the skilled artisan is able to obtain expression of a useful substance regardless of the substance produced or the animal in which the substance is produced. Thus, in order to use the full scope of the claimed transformant, the skilled artisan must extend the teachings of the specification---which are limited to general statements that the claimed transformants can be used to produce useful substances, an example of a cell line expressing G-CSF, and an example of a transgenic chicken expressing GFP—to obtain expression of a useful substance from any transformant.

With regard to practicing the broad scope of the claimed method, as it encompasses production of any useful substance comprising introducing the disclosed vector into the genome of a host cell, the teachings provided in the application are limited to those that would be useful in production of a protein in a cultured cell or the marker gene GFP in a transgenic chicken. Beyond the transgenic chicken expressing GFP which is reduced to practice (*Id.*) the specification is silent with regard to how one can generally obtain expression of any useful substance in any transgenic animal. Furthermore, to the extent that the claims encompass a method wherein production of the useful substance is part of a gene therapy method, the specification provides nothing more than a suggestion as to what diseases might be treated.

There is no discussion as to what genes will be administered or how they can be administered such that a therapeutic effect can be obtained. Thus, the skilled artisan seeking to practice the claimed method commensurate with its full scope must be able to extend the teachings of the specification—which are limited to an example of production of GFP in a chicken and production of G-CSF in a cultured cell, and general statements that other useful substances can be produced in other animals— such that a method comprising the steps of introducing a vector into a host cell can be used to produce any useful substance in any transgenic animal or to treat various diseases by gene therapy.

State of the prior art and level of predictability in the art: With respect to claim 8 as it encompasses any transgenic animal expressing any transgene, other than a transgenic chicken expressing GFP, the relevant art teaches that the phenotype obtained with one species of transgenic animal is not predictive of the same phenotype in another species of transgenic animal. When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (Sigmund (2000) *Artrioscler. Thromb. Vasc. Biol.* 20:1425-1429, page 1425, paragraph 1). Further, transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (Wall (1996) *Theriogenology* 45:57-68). Still further, the particular genetic elements required for optimal expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall; *supra*). Furthermore, the prior art teaches that the phenotype arising from insertion or deletion of even a

well-characterized gene is unpredictable. Doetchman (1999) *Lab. Animal Sci.* 49:137-143 teaches, "[o]ne often hears the comment that genetically engineered mice...are not useful because they frequently do not yield the expected phenotype, or they don't seem to have any phenotype. These expectations are often based on years of work, and in some instances, thousands of publications of mostly in vitro studies" (page 137, paragraph 1). Doetchman goes on to teach, "it has become clear that genetic background plays an important role in the susceptibility of mice to many disorders. Therefore, the phenotypes of knockout mouse strains will also have genetic background dependencies" (page 140, column 2, third full paragraph) and "[a]pparent lack of phenotype more likely reflects or inability to ask the right questions, or our lack of tools to answer them" page 142, first paragraph. These teachings point out that the phenotype arising from any given mutation or genetic manipulation of a transgenic mouse is highly unpredictable and in many cases requires empirical experimentation to uncover. Therefore, the skilled artisan must rely on the prior art and disclosure to teach a useful phenotype for each and every disrupted gene.

With regard to the production of useful substances in transgenic animals, at the time of the effective filing date of the instant application (i.e., 27 April 2000) the useful production of recombinant proteins in mammals was in an early stage of development. In reviewing the relevant literature, Houdebine (2000) *Transgen. Res.* 9:305-320 describes a myriad of obstacles that have been encountered by artisans seeking to express recombinant proteins in mammals at pharmaceutically relevant levels. In the abstract, Houdebine identifies three major sources of unpredictability in the art. First is the unpredictability of transgene expression; second is the unpredictability of proper posttranslational modification; and third is the unpredictable effects of

high-level recombinant expression on the host mammal. Significantly, in an article published at the time the instant application was filed, Houdebine teaches, "the mammary gland is presently the only really available animal bioreactor" (page 315, column 1, paragraph 7). Thus, at the time of filing, methods for useful production of recombinant proteins in mammalian organs and tissues outside of mammary gland were unavailable to the skilled artisan. With regard to production of pharmaceutical proteins in milk, Houdebine teaches, "numerous experiments have shown that the level and specificity of expression of a gene construct used as a transgene cannot be easily predicted" (paragraph bridging pages 309-310). In the paragraph bridging the left and right columns on page 311, Houdebine teaches that even the best mammary-specific promoters available as of 2000 provided inconsistent and unpredictable results when used for expression of recombinant proteins *in vivo*.

Houdebine points out that experiments carried out *in vitro* using cultured mammary cells are poor predictors of expression *in vivo*. In the third paragraph in the first column on page 314, Houdebine states, "[cultured mammary] cells can at best predict the intrinsic potency of a construct for transcription but not the level of expression in transgenic animals. The cell lines are not expected to be able to reflect all the events, which mature the proteins post-transcriptionally." Houdebine further teaches that proper posttranslational processing of proteins expressed at levels that would be considered useful is often unpredictable because the mechanisms are dependent on cellular enzymes that are present at variable concentrations in different cell types (paragraph bridging columns 1 and 2 on page 313). Importantly, because proper glycosylation is vital for pharmacological activity of many enzymes, Houdebine teaches that mammary cells do not always glycosylate recombinant proteins in an appropriate manner even when the protein is

naturally secreted in milk in a glycosylated form (see the example of bile salt-stimulated lipase presented in the second full paragraph in the right column on page 313). Houdebine teaches that the reasons why some proteins are not correctly glycosylated are particularly complex and might be related to the superphysiolgical production of the recombinant protein. Furthermore, in the paragraph bridging columns 1 and 2 on page 310, Houdebine teaches that obtaining high-level expression of proteins that are not naturally secreted is particularly problematic.

When viewed as a whole, the teachings of Houdebine, which are based on a review of the art at the time instant application was filed, clearly show that obtaining useful expression of a protein in a mammal was only enabled for a limited set of proteins in mammary tissues, and production of pharmaceutically useful amounts of any given protein in mammary tissue was unpredictable.

With regard to production of a useful substance in hen eggs, it is reasonable to expect that the sources of unpredictability encountered in more established transgenic bioreactor systems (i.e., unpredictability of transgene expression, unpredictability of proper posttranslational modification and unpredictable effects of high-level recombinant expression on the host animal; *Id.*) would also be encountered in birds. Furthermore, in an article published recently, Ivarie (2003) *Trends Biotechnol.* 21:14-19, teaches that expressing an protein at a useful level in eggs is particularly difficult because "[a] highly expressed oviduct promoter has not been developed" (page 16, second full paragraph in the left column). Further, Ivarie teaches "[t]he retroviral methods, although useful in proof-of-principle experiments, might not be able to deliver large enough constructs for high level, tissue-specific expression of pharmaceuticals in oviduct cells" (second full paragraph in the right column on page 17). Thus, Ivarie clearly teaches that

production of useful substances in hen eggs was far from routine at the time the instant application was filed.

With regard to the claimed method as it encompasses a method of gene therapy comprising producing a useful substance, at the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, regardless of the mode of delivery (e.g. adenovirus, retrovirus, liposome), was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) *Nature* Volume 389, page 239, column 3, paragraphe 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) *Science*, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin *et al.* further states in a report to the NIH that, " ... none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that, "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin *et al.* (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck *et al.* (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, Chapter 5, McGraw-Hill, NY, explains, "the

delivery of exogenous DNA and its processing by target cells require the introduction of new pharmakokinetic paradigms beyond those that describe the conventional medicines in use today". Eck *et al.* teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (see Eck *et al.* bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, "...the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph).

In an article published well after the effective filing date of the instant application, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches that the problems described above remained unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially "**3. Technical hurdles to be overcome in the future**", beginning on page 116 and continued through page 125).

Beyond the technical barriers common to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. The claims of the instant application are not limited to treatment of any particular condition and thus encompass methods of treating any and all conditions that might be amenable to gene therapy. However, Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic" (page 131, third full paragraph). Rubanyi states, "the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis for myocardial ischemia and peripheral vascular disease...) among multigenic diseases" (page 113, fourth paragraph). As of the filing date of the instant application, however, even these most promising areas presented barriers to successful gene therapy that could not be traversed by routine experimentation.

With regard to hemophilia, Schwaab *et al.* (2001) *Semin. Thromb. Hemost.* 27:417-424 teach that immune response against gene therapeutically administered Factor VIII and Factor IX compromised the success of therapy in many animal studies and that, "the situation is still more complicated by the fact that hemophilia B-affected dogs that have been intravenously treated with canine Factor IX protein without immune response against canine Factor IX develop antibodies when treated by gene therapy" (page 421, first paragraph in column II). Schwaab *et al.* also affirms that gene delivery remains a substantial problem in the development of gene therapy for hemophilia (see especially the second paragraph in column 2 on page 421). In subsequent discussion of ongoing clinical trials of gene therapy for hemophilia A and B, Schwaab *et al.* teach that, as of 2001, the effectiveness of gene therapy as a treatment for hemophilia had not been established (see beginning the final paragraph on page 421 and continued through the first paragraph of the second column on page 422). These teachings demonstrate that, as of the time of filing, successful treatment of hemophilia using gene therapy was unpredictable regardless of the delivery method employed.

With regard to gene therapy of ischemia, Rissanen *et al.* (2001) *Eur. J. Clin. Invest.* 31:651-666, teaches that although applications of therapeutic angiogenesis for ischemic disorders has established the proof of principle that exogenous growth factors can augment circulatory defects in animals and man, many important questions remain to be addressed. "Firstly, mechanisms of collateral growth by exogenous growth factors are still unclear...[a]dditional factors...may be required for collateral formation and maintenance of functional blood vessels. Secondly, the persistence of new vessels is unknown after transient gene expression. Thirdly, improvement is needed in gene transfer efficiency..." (paragraph bridging pages 659 and 660).

Emmanuelli *et al.* (2001) 133 :951-958 further teach that, "[d]elivery of angiogenic inducers...in ischaemic tissues allows rescue of blood perfusion. However, angiographic studies clearly show that the newly formed vasculature is abnormal and not well organized as in normal tissues...resembling the characteristics of leaky haemangiomas..." (page 955, the paragraph bridging columns 1 and 2). These teachings show that, even in an area of gene therapy considered promising, significant obstacles to successful therapy remained well after the effective filing date of the instant application.

Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, one of ordinary skill in the art would not be able to use the full scope of the claimed transformants or practice the full scope of the method of producing a useful substance without having to engage in undue experimentation. With regard to the transformant, the disclosure provides a vector that can be used to transform cells and make transgenic animals, and describes a transgenic chicken expressing a GFP reporter gene. These teachings fall well short of providing an enabled use for the full scope of the claimed transformant, which encompasses any animal transformed with any transgene. As the relevant art clearly teaches that the phenotype arising from any given genotypic manipulation of any given animal is unpredictable, the skilled artisan would not be able to use the full scope of those transgenic animals encompassed by the claim which have not already been reduced to practice

without engaging in empirical experimentation to construct and identify a useful phenotype for each one. Clearly this would require a level of experimentation that is well beyond the routine.

With regard to practicing the claimed method of producing a useful substance comprising transforming a host cell with the plasmid vector of the invention, the art also establishes that producing any substance in a transgenic animal or in a patient such that it is useful, either to be isolated for use as a pharmaceutical or directly useful as a therapeutic, is also highly unpredictable. As the teachings of the instant specification do nothing to address the sources of unpredictability in methods encompassing transgenic bioreactors (i.e., unpredictability of transgene expression, unpredictability of proper posttranslational modification and unpredictable effects of high-level recombinant expression on the host animal) and methods encompassing gene therapy (i.e., obtaining transgene expression at a therapeutic level and duration), practicing the full scope of the claimed method requires that the skilled artisan engage in empirical experimentation to provide the additional method steps required to obtain useful expression of each unique substance. Again, the level of experimentation required would be well beyond what is routine in the art.

For these reasons, the claims are not enabled beyond the scope of a transformant transformed with the plasmid according to claim 2, wherein said transformant is an isolated host cell or a transgenic chicken expressing a GFP transgene, or a method of producing a useful substance in a host cell *in vitro* or producing GFP in a transgenic chicken.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2, and all claims depending therefrom, are indefinite in the recitation of "when integrase" in the first line of (D3). It is unclear whether "integrase" is referring to the integrase of (D1) or some other integrase because it is not preceded by either a definite or an indefinite article.

Claims 1 and 2, and all claims depending therefrom, are further indefinite in the recitation of "the integration reaction" in the second line of (D3). There is no antecedent basis for "the integration reaction" in the claims.

The claims are further indefinite in that the metes and bounds of the integrase are unclear from the description thereof in the specification. In the description of (D1), an integrase is identified as "a protein produced in the cells infected with a retrovirus" and "[a]n integrase exists as a 36 kDa and a 32 kDa proteins in a virion...a gene encoding either of the two proteins can be used as the integrase gene" (page 27). These teachings seem to indicate that the integrase is limited to a specific 36 kDa or 32 kDa retroviral integrase. However, on page 32, the specification states, "[p]referably, integrase gene and LTR are derived from retroviruses", suggesting that the scope of the integrase is beyond retroviral integrases. For the purpose of examination, the integrase of the claims has been interpreted broadly to encompass any protein having integrase activity; however, clarification is requested.

Claims 2, 8 and 14 are indefinite in the inclusion of "any DNA segment to be integrated into the genome of host cells" in part (D4) of claim 2. The component (D4) is defined in the

paragraph bridging pages 32-33 as "any DNA segment to be desirably integrated into the genome of a certain type of host cells using the vectors of the present invention." As parts (D1), (D2) and (D3) all consist of DNA segments that will be integrated into the genome of a host cell, it is unclear how the limitation set forth as (D4) further limits the claim.

Claim 3 is indefinite in the recitation of "one LTR is joined to the other LTR" in line 3. There is no antecedent basis for LTR's in claim 1, from which claims 3 depends.

Claim 4 is indefinite in reciting that the DNA segments of (D2) and (D3) are situated within the region formed by the two LTRs joined together. As plasmid vectors typically exist in circular form, a segment positioned within a region formed by two LTRs joined together could be anywhere in the plasmid other than within the LTRs themselves. However, it would seem more likely that Applicant intends that the region be limited to a connecting sequence of terminal bases formed when one LTR is joined to another LTR as set forth in claim 3 and described on pages 29-30 of the specification.

Claims 6 and 7 are additionally indefinite in being directed to an integrase gene "derived from" viruses. Without a clear statement of the process by which the starting material is derivatized it is not possible to know the metes and bounds of such a limitation because any given starting material can have many divergent derivatives depending on the process of derivatization. Amending the claim to recite "isolated from" or "obtained from" instead of "derived from" would overcome this rejection.

Claim 7 is additionally indefinite in being directed to the plasmid vector "wherein the viruses belonging to Retroviridae comprise viruses belonging to subfamily Oncovirinae of Retroviridae". The claim reads as though limiting the family Retroviridae to comprising

Oncovirinae, which does not make sense in the context of the application. It would seem that Applicant is intending to limit the integrase gene obtained from viruses belonging to Retroviridae to an integrase gene obtained from the subfamily Oncovirinae. If this were Applicant's intention, amending the claim to read accordingly would be remedial.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by either one of Panganiban *et al.* (1983) *Nature* 306:155-160 (made of record in the Office Action mailed 16 July 2003; hereinafter, Panganiban '83) or Panganiban (1984) *Cell* 36:673-679 (made of record in the IDS filed 3 March 2003; hereinafter, Panganiban '84).

The art teaches a plasmid vector comprising the genome of the spleen necrosis retrovirus, which would comprise a native retroviral integrase gene and a region for controlling the expression of said integrase gene. The plasmids further comprise retroviral LTR's, which serve as integrase recognition regions when the retroviral integrase catalyzes the integration reaction (see especially: Panganiban '83, Figure 1 and the caption thereto; and Panganiban '84 Figure 1 (pPB101) and the caption thereto). The plasmid vector of the cited art thus teaches all of the limitations of claims 1 and 2 and the integrase, being a retroviral integrase, meets the limitations of claims 6 and 7. Further, the art teaches transformants transformed to produce retrovirus by

transfection of cells with the plasmid vectors according to claim 8 (see especially: Panganiban '83, Figure 3 and the caption thereto and Panganiban '84, the fourth full paragraph in the right column on page 674).

The plasmid vector and transformant taught by Panganiban '83 and Panganiban '84 are the same as those claimed in the instant application; therefore, the claims are anticipated by the prior art.

Claims 1, 2 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by VonMelchner *et al.* (WO 97/07223).

VonMelchner *et al.* teaches a plasmid vector comprising a Cre recombinase gene, a region for controlling the expression of the integrase gene and a segment of DNA serving as an integrase recognition region when the integrase catalyzes the integration reaction (i.e., lox site; see especially the paragraph bridging pages 14-15, and Figure 5 and the caption thereto). Thus, VonMelchner *et al.* teaches a plasmid vector comprising all of the limitations of the plasmid vector of claims 1 and 2. Further, VonMelchner *et al.* teaches transformants transformed to produce retrovirus by transfection of cells with the plasmid vectors according to claim 8 (see especially the paragraph bridging pages 14-15).

The plasmid vector and transformant taught by VonMelchner *et al.* are the same as those claimed in the instant application; therefore, the claims are anticipated by the prior art.

Allowable Subject Matter

Claims 3-5 and 15 are free of the prior art. Although the art of record teaches the plasmid vector of claims 1 and 2, the art does not teach or suggest the vector comprising both an integrase and a pair of LTR's joined together to form an integrase recognition region. Although Panganiban '84 teaches insertion of a tandem LTR into a plasmid vector (see pAP173 and pAP199), the integrase gene is disrupted in both of the plasmid constructs as evidenced by the requirement for helper virus. Panganiban '84 does not suggest constructing a vector comprising both an integrase and a tandem LTR and, as the art generally teaches that retrovirus protein encoding genes should be removed from retroviral vectors, the art does not provide motivation to modify the vector comprising the tandem LTR's of Panganiban *et al.* to include an integrase gene. The method of claim 15 is also free of the art because, although VonMelchner *et al.* teaches producing a useful substance wherein the disclosed vector is used to produce a retrovirus which is then introduced into a host cell, VonMelchner *et al.* does not teach a method comprising the steps of introducing a plasmid vector into a host cell and allowing the vector to integrate into the genome of the host cell such that a protein encoded thereby is expressed in the host cell to produce a useful product.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DMS

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER